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also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an mendment, effected by this office, following a request by the applicant and agreed to by the omptroller-General.

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Signed

Dated 25 July 2006

Patents Form 1/77

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P01/7700 0.00-0219512.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference ~~GMW/RAC/P19585GB~~ 00389/GB

2. Patent application number *(The Patents Office will fill in this)* 0219512.1 21 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Norton Healthcare Limited
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United Kingdom

Patents ADP number *(if you know it)* 6188221003

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention

Inhalation Compositions With High Drug Ratios

5. Name of your agent *(if you have one)*

ELKINGTON AND FIFE

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)* 67004

JPM 8/3/5

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing *(day/month/year)*
N/A		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of Filing *(day/month/year)*
N/A	N/A

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

See note (d))

Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	5
Claim(s)	2
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature: Elkington and Fife

Date: 21 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Gordon Wright
01732 458881

INHALATION COMPOSITIONS WITH HIGH DRUG RATIOS

This invention relates to dry powder inhalation compositions, their preparation and use. In particular, it is concerned with formulations of the medicament formoterol and pharmaceutically acceptable derivatives thereof mixed with particulate lactose.

In order to be able to be inspired into the key target sites in the lungs of patients, inhalation drugs are typically provided in micronized form with average particle sizes of up to 10 microns. A number of devices have been developed for assisting the delivery of such medicaments into the lungs of patients. In one sort of device, a dry powdered inhaler (DPI) device, the medicament to be inhaled is dispensed into an air stream produced by the inspiratory action of the patient. A large number of such devices have been developed. The device may be a single dose device (eg wherein drug is dispensed from a pre-metered dosage means such as a capsule) or multidose (where the drug is stored in a reservoir and then metered prior to dispersal in the air stream or where the drug is pre-metered and stored in multiple dosage packs such as blisters). In many (but not all) DPI devices, the particulate drug is mixed with an excipient powder of larger average particle size and the drug particles are blended with the excipient to create a generally homogenous mixture. The larger particle size of the excipient results in the powder mixture being flowable, and the homogeneity of the mixture enables it to be metered into accurately measurable doses. This is of particular importance when only very small quantities of the drug are required in a dose. Excipient powders of this kind, pharmaceutical powder compositions for inhalation utilising such excipients are described, for example, in US Patent 3 957 965.

The accurate metering of highly potent inhalable drugs causes particular problems, as the quantity of medicament in the composition relative to that of the carrier is likely to be particularly small. (Less than 1 part of drug to 50 parts of carrier). One such medicament is formoterol which is often administered to patients at a dose of less than 60 micrograms; doses may be as small as 6 micrograms. We have now found dry powder inhalation compositions of formoterol which can be accurately metered and at the same time give good dose uniformity when administered to patients, particularly when used in dry powder devices such as that described in WO 92/10229. In addition,

such compositions can give better dispersions when dispensed from such devices, then previously described compositions. Certain compositions may also be more stable.

According to the invention, we provide a dry powder inhalation composition comprising formoterol or a pharmaceutically acceptable derivative thereof as active ingredient and pharmaceutically acceptable particulate carrier, wherein the composition comprises at least 0.25% by weight of the active ingredient.

We prefer compositions which comprise less than 10% by weight of the active ingredient.

Preferred compositions comprise from 0.26 to 1% by weight of the active ingredient, more especially 0.265 to 0.5% by weight of the active ingredient.

Although a range of pharmaceutically acceptable particulate carriers are known for use in inhalation formulations, such as sugar, in particular di- and polysaccharides, we particularly prefer lactose, especially alpha lactose monohydrate.

In general, the particle size of the carrier should be such that it can be entrained in an air stream but not deposited in the key target sites of the lung. Accordingly, carrier, with volume median diameter (VMD) or mass median diameter (MMD) of less than 40 microns is generally excluded. We prefer the carrier, eg lactose, to have a VMD or MMD of from 50 to 250μm eg from 50 to 60μm or 60 to 90μm or 90 to 150μm.

The compositions of the present invention may be used in the treatment of chronic obstructive pulmonary disease.

The active ingredient may be in any isomeric form or mixture of isomeric forms, for example a pure enantiomer, particularly the R, R-enantiomer, a mixture of enantiomers, a race mate or a mixture thereof. Pharmaceutically acceptable derivatives of formoterol include pharmaceutically acceptable salts, in particular acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulphuric or phosphoric acid. The salt may also be with an organic acid such as acetic, sucinic, maleic,

furmaric, citric, tartaric, lactic or benzoic. The active ingredient and pharmaceutically acceptable derivatives thereof may exist in the form of a solvate, in particular a hydrate. A preferred form of active ingredient for use in the invention is formoterol fumarate, especially formoterol fumarate di-hydrate, conveniently in its raceimic form. Formoterol, salts and hydrates thereof and salt hydrates thereof as described above may be prepared by known methods, for example as described in US 3 994 974 or US 5 684 199.

In general, the active ingredient is present in the dry powder composition at an amount which is less than 10 %, preferably less than 2 % and most preferably less than 1 %. The actual amount of active ingredient in the composition will depend to a large extent on the nature of the dry powder inhaler and the quantity of composition that is metered individual dose. Where a large dose of composition is metered, the proportion of formoterol in the dose will be reduced. Particularly, dilute compositions are disclosed in WO 01/39745, for example 0.02 % by weight.

The mean particle diameter of the active ingredient is preferably up to 10 microns, more preferably up to 5 microns especially from 1 to 5 microns. The particle size of the active ingredient and of the carrier can be reduced to the desired level by conventional means, for example by grinding in a mill for example an air jet, ball or vibrator mill, by sieving, by spray-drying or by lyophilisation.

The dry powder composition may be metered and filled into capsules, eg gelatine or hydroxypropyl methol cellulose capsules such that the capsule contains a unit dose of active ingredient.

Doses of active ingredient to be held in accordance with the invention, may be in general from 1 to 60 micrograms. When the active ingredient is formoterol fumarate dihydrate, the dose may be, for example, from 6 to 54 micrograms. Preferred doses are from 6 to 24 micrograms, especially the unit doses of 6 micrograms, 12 micrograms and 24 micrograms. These doses may be administered once or twice daily.

When the dry powder is in a capsule containing a unit dose of active ingredient, the total amount of composition will depend on the size of the capsules and the characteristics of the inhalation device with which the capsules are being used. However, characteristic total fill weights of dry powder per capsule are between 1 and 5 mg.

Alternatively, the dry powder composition according to the invention may be filled into the reservoir of a multidose dry powder inhaler, for example of the kind illustrated in WO 92/10229.

Compositions according to the invention may be readily prepared by blending the required amount of active ingredient with the required amount of particulate carrier of the desired particle size distribution.

Example 1

0.265 grams of formoterol (as the fumarate dihydrate salt) was blended with 99.735 grams of lactose with VMD or MMD of 89-110 microns and a geometric standard deviation (GSD) of 2.2-4.9 and filled into the reservoir of a dry powder inhaler of the type illustrated in WO 92/10229.

The inhalers that contained the formulation were then tested for pharmaceutical performance under conditions specified in European Pharmacopoeia (2001). The drug per actuation (DPA) was measured using a dose unit sampling unit whilst fine particle dose (FPD) and fine particle fraction (FPF) were measured using a 5-stage liquid impinger

The compositions gave excellent dose uniformity when used in association with the device of WO 92/10229 which produced all mean doses within 80-120% label claim and overall relative standard deviation (RSD) < 15% (Table 1). The same products also result in over 40% drug particles having aerodynamic particle size < 5 microns,

suggesting that they are highly efficient in generating deeply inspirable drug . Typical in vitro deposition profiles are shown in Table 2.

Table 1. Dose consistency over life of IvaxIvax Formoterol MDPI, expressed as % label claim (LC)

Strength	Overall mean in mcg (RSD)	% mean doses within 85-115% LC	% individual doses within 80-120% LC	% Individual doses within 75-125% LC
6 mcg (n=930)	5.7 (13%)	95	93	96
12 mcg (n=500)	12.2(10%)	100	97	99

(n= number of doses. Ten doses from the beginning, middle and end of device life were collected from each inhaler).

Table 2. In vitro deposition profiles of formoterol from the IvaxIvax MDPI

Strength	RD (μg)	FPD (μg)	FPF (% RD)
6 mcg	5.0 - 5.9	2.4 - 2.8	48 - 48
12 mcg	11.1 - 13.4	5.4 - 7.2	49 - 54

RD - Recovered dose

FPD - Fine particle dose

FPF - Fine particle fraction

CLAIMS:

1. A dry powder inhalation composition comprising formoterol or a pharmaceutically acceptable derivative thereof as active ingredient and a pharmaceutically acceptable particulate carrier, wherein the composition comprises at least 0.25% by weight of the active ingredient.

2. A composition according to Claim 1, wherein the composition comprises less than 10% by weight of the active ingredient.

3. A composition according to Claim 1 or Claim 2, wherein the composition comprises from 0.26 to 1% by weight of the active ingredient.

4. A composition according to any one of the preceding Claims, which comprises from 0.265 to 0.5% by weight of the active ingredient.

5. A composition according to any one of the preceding Claims, wherein the carrier is lactose.

6. A composition according to any one of the preceding Claims, wherein the particle size of the carrier is less than 250 microns.

7. A composition according to any one of the preceding Claims, wherein the particle size of the active ingredient is less than 10 microns.

8. A capsule containing from 1 to 25 mg of a composition according to any one of Claims 1 to 7

9. A multidose dry powder inhaler including a reservoir containing from 5 to 50 grams of a composition according to any one of Claims 1 to 7.